Oxcarbazepine induced Stevens-Johnson syndrome and Toxic epidermal necrolysis overlap- A case report

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Abstract

Drug induced skin reactions although common with older epileptic drugs like phenytoin, lamotrigine, carbamazepine, the newer antiepileptic drugs are less likely to cause. Oxcarbazepine, the succeeder of carbamazepine has better safety profile with respect side-effects and adverse drug reactions. The Stevens-Johnson Syndrome, an adverse drug reaction is found to be less common and there were few case reports in literature with oxcarbazepine. Here we are reporting a case of oxcarbazepine induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) Overlap in line with CARE guidelines.

Introduction:

Drug induced cutaneous reactions can be mild or severe based on morbidity and mortality it possesses. While drug exanthem is the most common skin reaction to medications, it's not uncommon for the serious cutaneous drug reactions to ensue [1]. Steven-Johnson syndrome and toxic epidermal necrolysis are idiosyncratic drug reactions, which are type IV hypersensitivity reaction triggered by drug antigens in keratinocytes that induces T-cell mediated cytotoxic reaction[2]. SJS is characterized by skin lesions that can range from erythematous or purpuric papules to flaccid bullae and confluent erosions and can affect both mucosal and non-mucosal surfaces, predisposing patient to super added infections and toxic state. This potentially lethal drug reaction if involves $>$ 10% of body surface area is called SJS syndrome while when involving more than 30% of BSA is called Toxic epidermal necrolysis[3].

Sulfonamides, nonsteroidal anti-inflammatory drugs, anticonvulsants and antibiotics are the commonly implicated drugs in SJS and TEN. And among antiepileptics, carbamazepine (CBZ) is one of the culpable agents implicated[4]. The 10-keto analogue of carbamazepine, Oxcarbazepine (OXC) has better safety profile compared to predecessor and hence preferred in elderly and children. The Stevens-Johnson Syndrome, an adverse drug reaction was found to be less common with oxcarbazepine and there were only few case reports in the literature[1,2,5-7]. Most of Adverse drug reactions are under-reported, thus resulting in no evaluation of the expectedness, severity and causality of these reactions[8]. Thus, it is important to report such drug reactions as it will further help in estimating the incidence of oxcarbazepine induced SJS. Here we are reporting a case of oxcarbazepine induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) Overlap.

Case report :

A 76-year-old female was brought to emergency department of AIIMS, with Chief complaints of dusky red macules all over body, including perioral skin with erosion in buccal and palatal mucosa with white exudate and erosions on bilateral eyelids. She has had history of insomnia and agitation one month back for which escitalopram, lorazepam and amantadine were prescribed, which was taken for a week and was discontinued because of worsening of agitation, increased talkativeness and psychomotor activity. And after two weeks, she was further taken to a private practitioner for the same symptoms and was prescribed oxcarbazepine

in 600mg dosage, following which there was resolution of symptoms. Post 1 week of starting of the above medication she developed mild fever, macular rash over trunk with perioral rashes. The next day the patient's attendants noticed blister formation on sides of mouth and macular eruptions on thigh, spreading to all over body and face with redness of eyes and painful mouth ulcers with difficulty in eating food over the next 3 days. For which they discontinued the medication and visited the casualty and patient was admitted. Dermatological examination revealed 20 percent body surface area involvement with erosions in oral mucosa, bilateral eyelids, back and confluent macular eruptions over trunk and thighs as shown in figure 1,2& 3. She had no history of any allergies, drug reactions. There was no associated swelling of the joints or any other tissue involvement. There was mild local raise of temperature with stable vitals and other systematic examination was within normal limits. There was no history of any recent use of cosmetic products or any local application of cream/lotions on face or food changes or any other medication. Laboratory investigations showed significantly anaemia, increased ESR, raised blood glucose levels, neutrophilia, lymphocytopenia, normal liver function tests and renal function tests but low serum sodium.

During the course in hospital, patient was started on cyclosporin and tapering dose of dexamethasone. She had an episode of disorientation which was managed with low dose haloperidol. She was given adequate antibiotic coverage with blood sugar and pain management. She responded well to treatment and was discharged on 5^{th} day of admission with dried erosions and healing lesions.

This case had a Naranjo score of +8 based on available clinical information that points towards probable adverse drug reactions as we did not attempt to re-challenge with the oxcarbazepine for any reappearance of the rash[9]. It was an ADR that required admission increasing length of stay in hospital with the treatment and stoppage of suspected drug as per assessment with Hartwig's severity scale that revealed a level 4 severity[10]. The WHO-UMC criteria for causality revealed this ADR as being probable/likely due to oxcarbazepine intake[11]. A SCORTEN scoring system for SJS/TEN predicts the probability of hospital mortality was calculated within the first 24 hours of admission revealed a score of 3(Age>40, epidermal detachment >10% at the admission, blood glucose >300mg/dl) [12].

Discussion:

There are two types of ADR based on expectedness of adverse drug reactions, Type A ADRs which are pharmacologically predictable and Type B ADRs which are idiosyncratic[8]. They are described and classified by the percentage of body surface area (BSA) involvement with less than 10% in SJS, 10% to 30% in SJS/TEN overlap and more than 30% in TEN[12]. This case with 10-30% BSA involvement is an SJS/TEN overlap due to oxcarbazepine and a Type B ADR and also defined as a severe cutaneous adverse drug reaction (SCAR). The pathophysiological mechanism behind SJS/TEN is conceptualised to be a type IV hypersensitivity reaction due to binding of drug to Major Histocompatibility complex I that results in cytotoxic CD8+ T cells mediated destruction of lower layer epidermis[13]. The activated antigen driven CD8+ T cells in the epidermis produce cytolytic peptides such as granulysin, a cytolytic peptide that leads to keratinocyte death[13,14]. There is a strong genetic association with HLA-B*1502 allele and carbamazepine SJS/TEN, which is widely seen in Southeast Asia population led to recommending the individuals of Asian ethnicity to be genotyped for the presence of the risk allele before receiving carbamazepine by The Food and Drug Administration. However, HLA-B*15:02 is less strongly associated with oxcarbazepine SJS/TEN with a significantly lower Positive Predictive Value of 0.73 and >5000 patients would need to be tested to prevent one case of SJS/TEN[13].

There had been lesser incidence of SJS reported with Oxcarbazepine but there is reportedly more incidence of drug rashes and SJS in patients who are hypersensitive to CBZ pointing towards cross-sensitivity. This cross sensitivity may be due to the dibenzazepine ring which is the common structure in CBZ and OXC[15]. In our patient there was no previous recorded hypersensitivity to any drugs. Here it is also interesting to note that our patient had SJS within one week of starting the incriminated drug which may be due to her older age.

In conclusion, Steven Johnsons syndrome due to oxcarbazepine is rare but still happens nevertheless. SJS

being a life-threatening adverse effect, clinicians should be aware and vigilant about the same while starting a patient on OXC and should be prompt in withdrawing the agent at first sight of any cutaneous reaction. Patients should also be informed in detail about the same and encouraged to report back in case of adverse effects. Thus, studying and reporting of ADRs associated with any drug is also vital for estimating their incidence, expectedness, severity, morbidity and mortality in clinical practice and further determining the predisposing risk factors.

Conflict of Interest

None declared.

Author Contributions: All authors were involved in the clinical management of this patient and contributed to the concept, design and preparation of this manuscript.

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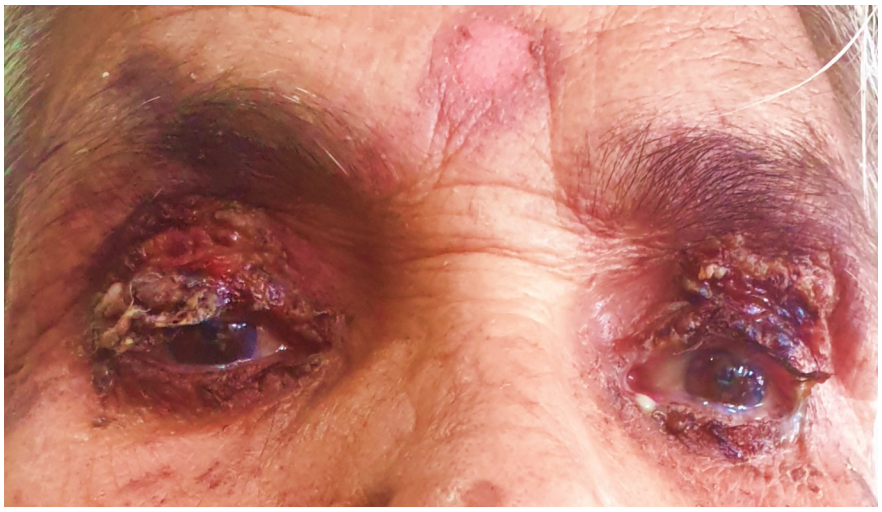
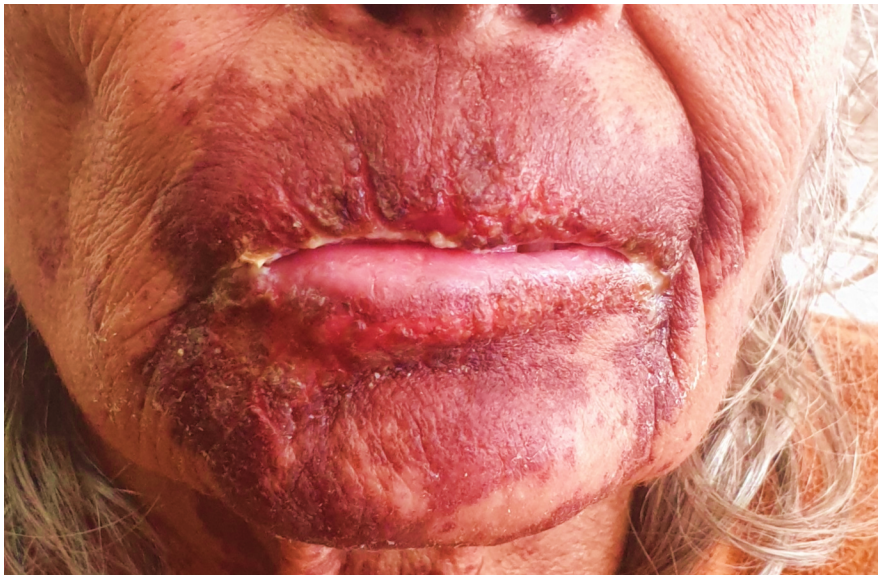
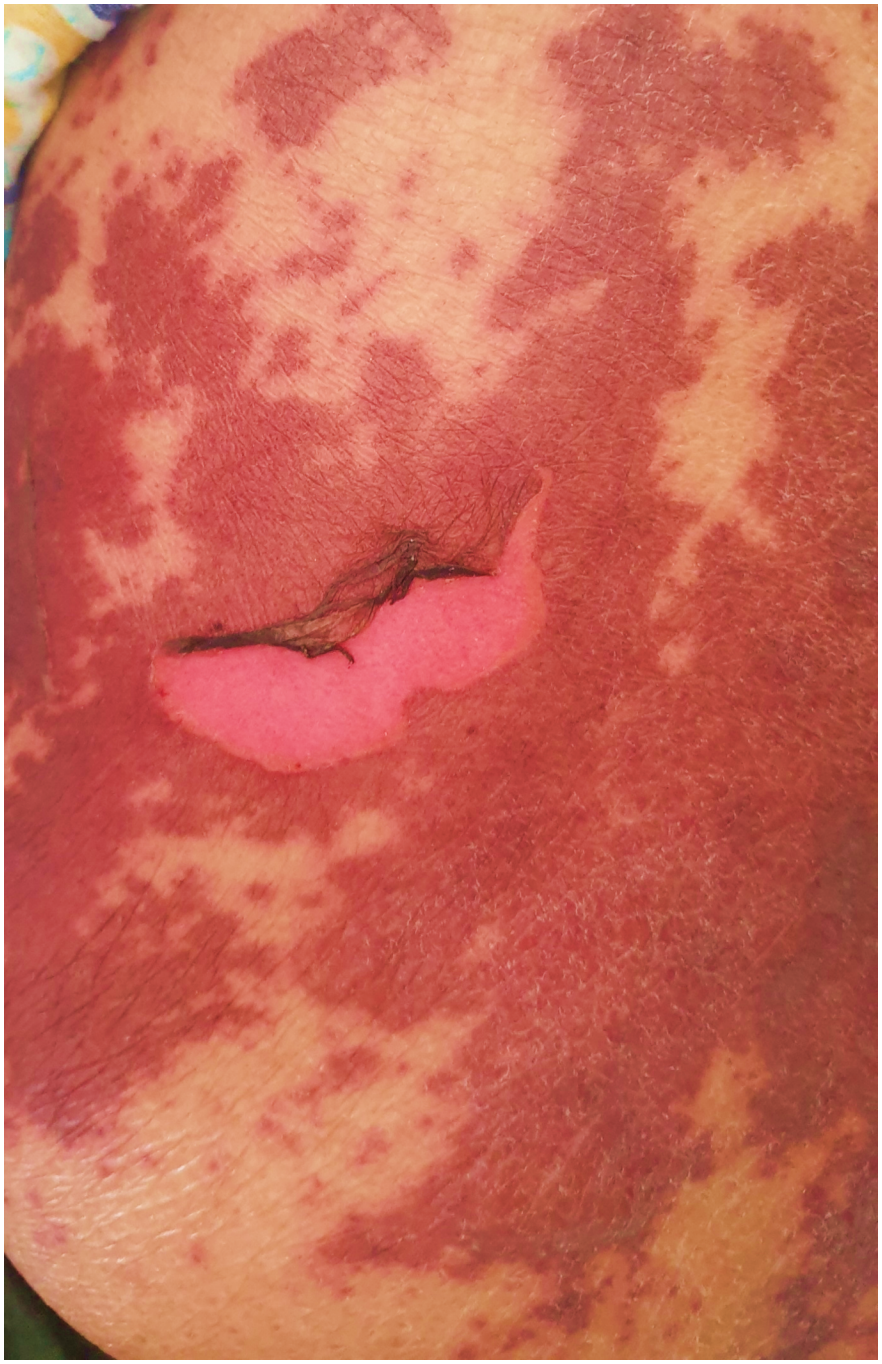
Figures :



Figure



Figure



Figure

Figure legends:

1. Figure 1 showing erosions and crusting of bilateral eyelids and purulent discharge from eyes
2. Figure 2 showing the erosions in perioral area with crusting extending to neck
3. Figure 3 showing the red macules all over the trunk with sloughing and positive Nikolsky sign